MANAGEMENT OF THE ANEMIAS IN INFANCY AND CHILDHOOD*

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THE reawakening of interest in hematology following the discovery of the therapeutic use of liver in pernicious anemia was not without its influence in stimulating the investigation of blood diseases in infancy and childhood. It is the purpose of this presentation to discuss the management of the blood diseases peculiar to infancy and childhood in the light of recent advances. Since a predominant characteristic of the blood reactions of childhood is the tendency to revert under stress to embryonic blood formation, this discussion may start from that point.

FETAL BLOOD FORMATION

Blood formation occurs initially in the wall of the yolk sac and is then assumed by the mesenchymal cells throughout the human embryo. In the sixth week, the liver becomes the site of red cell multiplication and the spleen participates in this function by the end of the second month. In the second and third months, the thymus, mesonephros and the lymph nodes become additional sites of blood formation. While the bone marrow makes its appearance in the sixth week, it becomes actively engaged in hematopoiesis in the third month. During the course of fetal life all of these organs manufacture blood cells with the major activity residing in the spleen and liver. The bone marrow at birth takes over the hematopoietic role of the liver and spleen but in infants and children, when the usual blood sites are strained, compensatory hematopoiesis occurs quite readily in the fetal blood forming organs. The potentiality of blood formation in extramedullary sites persists throughout life, although it is less likely to occur the further the individual is removed from early infancy.

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The Bone Marrow in Infancy and Childhood
Clinical Implications

So active is the demand for blood cell formation in the infant and young child that all the bones are filled with red marrow. At about seven years of age fat appears, which is grossly observed at puberty. It is only with the appearance of non-functioning yellow marrow that a potential reservoir is created for blood formation when the demand for blood regeneration is increased. In early infancy with the absence of reserve marrow, the need for increased blood formation arising from anemia due to infection or associated with specific blood diseases may necessitate the reactivation of extramedullary fetal sites. Beyond this, when there is need for further room for blood formation, the marrow expands by absorption and atrophy of bony trabeculae and of the cortex. These changes may be sufficiently marked to be visualized roentgenographically as are observed in Cooley's anemia, sickle cell anemia and acholuric jaundice.

The encroachment upon the actively functioning marrow by leukoblastic cells within the inelastic bony skeleton accounts for the bone and joint pain encountered in some instances of leukemia in childhood which makes the clinical differentiation from rheumatic fever so difficult.[1] The roentgenogram, however, often throws light upon the underlying pathological process and discloses generalized or local rarefaction, focal areas of bone absorption and of periosteal elevation. In a study of the roentgenographic changes in childhood leukemia, Baty and Vogt[2] found in 70 per cent of their cases a narrow, transverse zone of rarefaction just proximal to the metaphysis of the long bones, most marked in the lower end of the femora and tibiae. This line may be observed in other conditions, but we have found it a valuable diagnostic aid, particularly when leukemic cells are not yet greatly increased in the peripheral blood.

Hematopoietic Factors in Treatment of Anemia

In treatment it is important to remember that the erythrocyte-maturing factor found largely in the liver is required for the transition of megaloblast to normoblast. For the final maturation of the erythrocyte iron, copper, vitamin C and thyroxin are probably necessary and for hemoglobin regeneration iron and copper are required. Cobalt

and manganese have also been shown to influence hemoglobin formation but save for iron none of these metals appear in the hemoglobin molecule and probably serve their function as catalysts. In all age groups transfusion constitutes an important element in treatment of anemia by elevating the hemoglobin and red cells, relieving toxemia, reinforcing the supply of hematopoietic principles present in the plasma which control blood formation, and stimulating their normal production. It should be remembered that the completely functioning hematopoietic activities of the adult are not present at birth but develop gradually. To maintain the balance between blood production and blood destruction, maturation and antihemolytic factors are gradually elaborated by the infant and child and until this is accomplished dependence upon fetal stores may be required. It is conceivable, also, that in some infants the development may be slow, and when this is markedly retarded it may account in part at least for such conditions as are included in the syndrome of erythroblastosis fetalis. In accordance with this concept, when prothrombin formation is greatly delayed in the newly born, hemorrhagic disease occurs. It is possible that transfusion stimulates the production of these elements in the infant by acting as an accelerating force in the same manner that it hastens the development of the final blood groups in the young infant. It is possible that frequent transfusions of small quantities of blood may serve the purpose of stimulation more effectively than larger transfusions at longer intervals.

Clinical classifications of anemia are usually based on the predominance of either decreased red cell formation or increased red cell destruction. It will be noted in this presentation that evidences of both deficient blood formation and increased blood destruction may be manifest in the same disorder, although one of these may dominate the clinical picture at a particular time. For that reason there are many anemias which do not yet permit of unequivocal assignment to a definite category such as can now be done with pernicious anemia or with the hypochromic anemia of infants. With Cooley's anemia and in erythroblastosis fetalis, for instance, there have been controversial claims as to classification and until a curative agent is available it will not be possible to settle this problem definitely.

In now taking up the various blood disorders, I should like to point out that in the time allotted it will only be possible to emphasize the

highlights of their diagnosis and treatment since each of these has in recent years become the subject of extensive investigation.

Erythroblastosis Fetalis

Among the blood dyscrasias of the newborn none has afforded more interest in recent years as regards diagnosis and etiology than the symptom complex of erythroblastosis fetalis. The diseases comprising this group consist of hydrops fetalis, icterus gravis and anemia of the newborn. Although they present a varied clinical picture, they are linked together by certain common features: namely, fetal type of extramedullary hematopoiesis, abnormal numbers of nucleated red cells in the circulating blood, edema, jaundice, and the fact that successive newborn siblings may be affected by one or the other of these conditions. The gradation of one member of this group into another has been repeatedly demonstrated by cases of icterus gravis with severe edema, and by milder cases of this condition, which during the recovery phase are almost indistinguishable from congenital anemia.

The prognosis of erythroblastosis fetalis is gravest when the signs of the disease are fully established at birth. Cases of hydrops fetalis are usually still-born or die soon after birth, although borderline cases with less extensive edema may survive.[3] When the clinical and hematologic features of icterus gravis are fully established at birth, especially when the jaundice is severe, the outlook is more doubtful than if the disease develops in the course of the first few days of life. With earlier diagnosis and prompter treatment, the mortality from this condition has been drastically reduced.

The most satisfactory treatment of this syndrome consists of transfusion of blood by the intravenous route. The amount of blood with most young infants approximates 20 cc. per kilogram of body weight for each transfusion. It is important to remember that this condition is self-limited and transfusions are supportive in the sense that they tide the infant over the acute stages of the disease until normal blood formation is established. While repeated transfusions are usually required, the intervals between them depend upon the clinical condition of the patient and the state of the blood. Experience has shown that it is unnecessary to attempt to maintain the high hemoglobin and red cell levels which characterize the blood of the normal newborn. Icterus gravis and anemia of the newborn often follow a protracted course and counts

of 2.5 to 3.5 million red cells per cmm. have been found entirely compatible with the well-being of the patients. Unless transfusions are carefully timed, excessive injections of blood may aggravate the hemolytic process instead of checking it. When an infant with a severe form of icterus gravis also presents evidence of toxemia, transfusion should be supplemented by the administration of parenteral fluids.

It has been suggested that an anti-hemolytic substance supplied in utero by the mother controls the hemolysis of red cells in the fetus.[4] With the idea that the infant with erythroblastosis fetalis lacks this principle, injections of serum or plasma from a healthy adult, who presumably possesses this substance, have been advised. Injections of plasma or serum intravenously or intramuscularly, preferably the former, may be useful under certain circumstances. Occasionally an infant at birth possesses normal levels of hemoglobin or red cells but the blood may reveal abnormal numbers of nucleated red cells and the clinical appearance strongly suggests icterus gravis. The introduction of whole blood may still further increase the polycythemic values of the newborn. In such a case the plasma derived from the blood, which would ordinarily have been transfused, may be injected intravenously. The disease at times may show no further progression and recovery occurs. Where possible, it is good practice to give at least one transfusion in addition to the serum injection in order to anticipate any inordinate drop in red cells.

Serum has also been found useful in later stages of icterus gravis and anemia of the newborn at a time when the two conditions simulate each other so closely. Repeated transfusions in the second month of the disease are usually found to be only temporarily effective in elevating the blood levels, whereas repeated intramuscular injections of serum in doses of 10 to 15 cc. are simpler and in some instances have proven of decided value. In the acute stage of the disease, serum or plasma injections are to be regarded as accessory to transfusion and not a substitute for it.

While liver extract has been valueless during the early and acute stages of erythroblastosis, it has been useful during the more chronic stage of the anemia, particularly in those instances when the red cells are still dominantly macrocytic. The liver extract to be employed should not be too highly refined and a cruder one in which each cc. contains no more than two or three units is preferable. The liver is administered intramuscularly in 1 cc. dosage and the number of injections must vary with every case and depends upon the hematologic response.

Hemorrhagic Disease of the Newborn

In addition to the disorders involving red cell maturation and of the forces controlling hemolysis, the factors involved in the clotting of blood may also be affected during the neonatal period and this disturbance is manifested in the clinical condition known as hemorrhagic disease of the newborn.

The tendency to bleed is the result of factors which are operative in the neonatal period. Normally, the coagulation time of the blood is considerably prolonged in the first four or five days of life. Hemorrhagic disease of the newborn must depend, therefore, on impairment in the coagulation mechanism which exaggerates this normal prolongation.[5] Many studies suggest that the clinical manifestations of hemorrhagic disease depend on an abnormal lowering of prothrombin levels which are already reduced physiologically. Bleeding does not occur more frequently because of the rapid conversion of prothrombin to thrombin which compensates for the quantitative deficiency in this substance.

Treatment until recently has consisted almost entirely of blood transfusions. Intramuscular injections of blood have been employed in prophylaxis but their value has been difficult to assess. On the other hand, with the first evidences of bleeding in the newborn the need for blood is urgent and it may be obtained at once from the father or mother and injected without preliminary blood grouping, 10 cc. into each buttock. Any improvement which results must come from the plasma components and products liberated from the disintegration of red cells.

The most effective method of giving blood, however, and the one to be preferred is by the intravenous route, and the dosage is 20 cc. per kilogram of the infant's body weight. The loss of blood may be severe and the anemia may become profound, but the favorable effects of transfusion result not alone from the replacement of red cells, and of hemoglobin, but of prothrombin and of other factors contained in the plasma whose deficiency may contribute to the pathogenesis of the hemorrhage. It tides the infant over until the fundamental disorder corrects itself in the course of development.

With the more recent knowledge that hemorrhagic disease is associated with a deficient prothrombin content of the blood and that vitamin K influences its formation, the most effective plan of treatment consists of combining transfusion with the administration of vitamin K.

Vitamin K is a fat soluble substance whose absence in the diet of chicks was observed by Dam to produce a hemorrhagic disorder. The lowered clotting time of the blood of the chick was soon found to result from a deficiency in prothrombin. Studies following this discovery have eventually resulted in the isolation and synthesis of various substances possessing vitamin K activity. At present the disorders in which vitamin K has been found most useful consist of obstructive jaundice and of hemorrhagic disease of the newborn, both of which are associated with a lowered prothrombin content of the blood.

Several procedures have been followed, directed towards increasing the prothrombin level of the blood of the newly born infant. Vitamin K has been administered to the mother during the last weeks of pregnancy, just before the onset of labor and even during delivery.[6,7,8] This method has resulted in the elevation of both the prothrombin content of the blood in the mother and that of the newborn. Vitamin K has also been directly administered to the normal baby for several days after birth for prevention of bleeding, as well as in treatment of the infant who presents the first evidence of bleeding.

The form and dosage in which vitamin K is to be prescribed have varied a great deal because of the multiplicity of products now available and because of their varied strength. Waddell and Guerry[9] found increased prothrombin levels in newborn infants when they were given a vitamin K concentrate, Klotogen, orally in dosages of 1 cc., 0.5 cc., 0.5 cc., on the first, second and third days, respectively. They found that the same product given to the mother before delivery resulted in an elevation of the prothrombin content of the blood of the infant.

Of the synthetic vitamin K substances, the most active compound to date is 2-methyl-1, 4-naphthoquinone, first reported by Ansbacher and Fernholz.[10] This product has been administered in 1 mg. dosage to mothers before delivery with a resulting increase in the maternal plasma prothrombin as well as that of the infant. It has been given in smaller dosage to the newborn infant, namely, 0.5 mg. for the first 3 days of life, with the same results. This product has also been employed therapeutically in bleeding in the newborn with favorable clinical results. Recent studies have shown that vitamin K preparations may also be administered intramuscularly and intravenously with a resulting increase in the prothrombin content of the blood which is maintained. Whether or not vitamin K administration will be employed as a routine

measure in prophylaxis of this disease awaits the results of extensive trials now in progress.

Nutritional Anemia

Following the neonatal drop, hemoglobin reaches its lowest level at six weeks to two months of age and remains fairly constant for the remainder of infancy. During the first two years of life the hemoglobin normally ranges from approximately 10 to 12 grams per 100 cc. of blood (equivalent to 70 to 80 per cent).* Nutritional anemia describes the state of the blood in which the hemoglobin values fall consistently below the lower limit.

The period between 8 months and 2½ years constitutes a most critical period for the development of hypochromic anemia.[11] Hypochromic anemia occurs in childhood beyond the period of infancy when growth is again more rapid and the demand for iron is excessive, and this is noted during the period of puberty and especially in girls with the onset of menstruation. In the infant as well as in the older child the problem of treatment involves an inherent difficulty which arises from the lack of data as to the optimum hemoglobin value which will promote maximum growth and development.

The blood of the full-term infant of average birth weight and in good nutrition as seen in private practice usually possesses an average hemoglobin content of 11 gm. (75 per cent) or more after the neonatal period. For practical purposes, therefore, the value of 11 gm. should be designated as the lower limit of normal, although this is an arbitrary figure since it is not unusual to encounter infants, particularly prematures or twins, who are normal in every respect but whose hemoglobin after the second month falls below this value. Particular attention to the hemoglobin level should be directed to all infants who are growing rapidly, to prematures and twins, to those troubled by frequent infections and by gastrointestinal disturbances, and to those whose mothers during the latter part of pregnancy were known to have suffered from severe anemia. With premature infants and twins, it is a good plan to institute hemoglobin estimations during the second month of life and with normal full-term infants these may be postponed until the end of the second or third month.

The choice of iron preparations for the infant as for the adult

* Hemoglobin standard 100 per cent = 14.5 gm. per 100 cc. of blood.

depends upon their acknowledged activity, ease of administration, tolerance, inexpensiveness and solubility. The latter consideration applies particularly to the infant since inorganic salts that are readily ingested by the adult may be unsuitable for the infant. The iron salt should be preferably soluble so that it may be administered in water, milk, or a fruit juice. Reduced iron and saccharated ferrous carbonate possess the disadvantage of requiring a suspension because of their insolubility, but they can be offered to older children. Although there are several soluble iron salts suitable for use in infancy whose efficacy has been amply demonstrated by capable observers, my own experience has been with two of these salts, namely, iron and ammonium citrates and ferrous sulphate. Iron and ammonium citrates may be dispensed in a 10 per cent strength stock solution or in capsules containing the powdered scales. For the infant, the latter are opened before feeding and the contents dissolved in milk, water or sweetened orange juice. It is advisable to offer a small dose of only 5 grains at the outset, since at times vomiting or diarrhea follow its use. In the infant with nutritional anemia of a moderate grade the desired hemoglobin level can be obtained usually with a daily dose approximating 1 grain of iron and ammonium citrates per pound of body weight, which usually amounts to 15 to 30 grains.

Recent studies have shown that iron is more readily absorbed from the intestinal tract in its bivalent form,[12] and that the soluble ferrous salts are most active in synthesizing hemoglobin. Of these, ferrous sulphate has come into popular use, and dosages of 6 to 8 grains daily have been sufficient to produce satisfactory reticulocyte responses and the restoration of normal hemoglobin, red cell and hematocrit levels within a period of from 2 to 3 weeks in infants and young children. It is prescribed in infancy in the form of an elixir, each teaspoonful containing 2 grains of this salt, and the total dose is 3 to 4 teaspoonfuls daily. This dosage of iron we have found on many occasions has served a diagnostic purpose. When 6 to 8 grains of ferrous sulphate daily are administered to an infant or young child with anemia of moderate severity, the absence of a reticulocyte response and a failure of the hemoglobin to return to a level of about 11 gm. per 100 cc. of blood in from 2 to 3 weeks suggest continued severity of an infectious process or that the diagnosis of anemia on a purely nutritional basis is to be questioned. Using this principle, we have been able to uncover several cases of Cooley's anemia in early infancy when no other clinical features had as yet appeared.

With increasing age, the need for iron administration must be gauged in the light of the changing hemoglobin levels of normal children. Hemoglobin levels of 12.5 to 13.5 gm. per 100 cc. of blood are desirable and can be achieved by adequate anti-anemic therapy. The daily dose of ferrous sulphate in older children ranges up to 18 grains, although 9 to 12 grains are usually adequate, and of iron and ammonium citrates up to 90 grains. Because of individual variations in absorption, it must be emphasized here too that the simplest guide to adequate iron intake can only be obtained by repeated hemoglobin examinations.

When maximum doses of iron are required in a child to secure normal hemoglobin levels it may indicate inadequate absorption resulting from diminished or absent free-hydrochloric acid in the stomach. Normal gastric acidity is necessary for optimal absorption of iron from foods and iron preparations in all age periods, and hypoacidity may be a conditioning factor leading to iron deficiency anemias. While this condition has been well known as a factor in the pathogenesis of "idiopathic" hypochromic anemia in older individuals, its existence in children requires emphasis. Many studies have shown that in infants and in children defective gastric secretion is often associated with iron deficiency anemia and that this abnormality persists even when the anemia is cured. It is well known from adult experience that larger doses of iron are required for hemoglobin synthesis in individuals with achlorhydria than in those with normal gastric secretion. Children whose gastric secretion lacks acid should also be watched more closely for recurrence of anemia. There is a gap in our knowledge as to the onset of achlorhydria in those adults who develop idiopathic hypochromic anemia and pernicious anemia. The infants and children with deficient gastric secretion, particularly those who secrete no acid following histamine, may constitute the group of potential cases of these conditions in later life. The administration of hydrochloric acid is without value, however, in facilitating cure of the anemia and produces no response of the marrow as indicated by reticulocytosis.[13]

Increasing evidence points to the desirability of including an adequate quota of vitamins to assure the complete functioning of the manifold hematopoietic phases. In some cases complete recovery has been reported when yeast was employed as a supplement to iron,[14] and recent studies[15,16] indicate that components of the vitamin B complex are involved in hematopoiesis.

Since iron is absorbed in the ferrous form, the reduction of ferric salts to the bivalent form depends upon reducing mechanisms present in the small intestine. It has recently been shown that the administration of cevitamic acid with iron salts aids the absorption of iron probably by exerting a reducing action on ferric salts and by preventing the conversion of ferrous salts to the ferric state.[12]

In our experience it has not been necessary to employ copper in the treatment of nutritional anemia, although there are studies to show that its addition in minute traces results in prompt acceleration of hemoglobin production from a previously stationary level.[17] In the occasional infant in whom copper deficiency may occur, as evidenced by a refractory state of the anemia, minute amounts of this element, 1 mgm. daily (equivalent of 4 mg. of copper sulphate) may be included in the iron prescription.

Cooley's Anemia

Fifty years ago, von Jaksch described a condition occurring in infants which he designated as pseudoleukemic anemia whose distinctive features included a severe anemia affecting red cells and hemoglobin, extreme degrees of leukocytosis, occasional enlargement of the lymph nodes, slight increase in size of the liver and a marked splenomegaly. He differentiated this disorder from the anemia of rickets which showed a lesser degree of leukocytosis and particularly from leukemia with which it might most often be confused. He pointed out that the outcome in the disease he described may be favorable. Although von Jaksch separated pseudoleukemic anemia from the anemia of rickets and emphasized the features of marked leukocytosis in the former, many poorly defined anemias of infancy and childhood were gradually placed in the category of von Jaksch's anemia which were very often associated with infections, rickets, syphilis, and nutritional deficiencies.

In 1925 and in 1927, Cooley and his associates drew attention to an anemia which had heretofore been regarded as belonging to the heterogeneous group of von Jaksch's anemia, but which possessed such well-defined features as to constitute a definite clinical entity. Outstanding characteristics are its racial and familial tendencies, the skeletal changes, and the appearance of large numbers of circulating normoblasts.

With few exceptions, an important diagnostic feature of this condition has been its racial limitation to children one or both of whose

parents were born in northern Mediterranean countries, especially Italy, Greece, or Syria, and most frequently in Sicily. The disease begins insidiously early in infancy and is usually sufficiently advanced in the second year so that it can be recognized clinically. In severe cases the disease is fully developed early in life and its course is relatively short. Milder cases pass unrecognized until later childhood. There is evidence that, like hemolytic jaundice, it can occur in healthy members of the family in latent form so that inheritance is a possibility. It is also possible that there are individuals with mild forms of this disease who may perhaps be suffering with an unexplained low grade chronic anemia. This disease has been referred to as the erythroblastic anemia of Cooley, or from its racial limitation the term, Mediterranean anemia or thalassemia was suggested by Whipple and Bradford.[18]

In its fully developed form the symptoms are pallor, weakness, headache, bone pains, bouts of fever, anorexia and vomiting. The abdomen protrudes when splenomegaly becomes pronounced; the liver is enlarged to a lesser degree and lymphadenopathy is slight. Other important features include frontal and parietal bosses, prominent malar eminences, depression of the bridge of the nose, from which epicanthal folds arise lending an oblique appearance to the eyes, enlargement of the superior maxilla so that the lip is pushed upward often exposing the upper teeth, a muddy yellow complexion, prominent eyes whose sclerae may show a tint of icterus which is intensified at times. These characteristics combine to lend a mongoloid appearance to the patient and account for well-known resemblance of the affected children to each other rather than to their normal sisters and brothers.

The blood shows a moderate to severe anemia, leukocytosis, often with early myeloid cells, a reticulocytosis, an elevated icteric index, numerous nucleated red cells which are remarkably increased after splenectomy and a striking resistance of the red cells to hypotonic saline in fragility tests so that in some instances the red cells are not entirely hemolyzed even in distilled water.

In established cases of Cooley's anemia, in addition to erythroblastosis the red cells manifest polychromatophilia, poikilocytosis and anisocytosis. While variously shaped microcytes are present, the most important for diagnostic purposes are macrocytic cells containing little hemoglobin which appear in great numbers and whose size is sometimes of unusual proportion. At least three types of macrocytic red cells

characterize the blood in the various clinical types of Cooley's anemia but all types possess the fundamental characteristics of the red cells in this disease; namely, abnormal thinness. One of these is a non-specific type designated as a target cell, named so by Barrett[19] because of its deeply stained center and periphery which are arranged in concentric light and dark zones. The second type of macrocyte is usually a round or sometimes slightly oval cell with a narrow rim of hemoglobin of varying thickness with a large zone of central achromia in which a faintly stained island of hemoglobin may occasionally be discerned. The third or most specific type is a large, pale erythrocyte described by Cooley which contains irregularly distributed hemoglobin which is clumped and whose intervening areas seem to possess staining defects. This cell is extremely thin and leaflike and in wet preparations its edges are observed to fold over and the several layers thus formed possess a remarkable transparency.

X-rays of the skeletal system reveal the evidence of extreme hyperplasia of the bone marrow by osteoporosis, thinning of the cortex, trabecular atrophy, coarse reticulation with the regeneration of new bone, which is a later development in the disease, and thickening of the skull. Caffey[20] found that the frontal bone was the site of early and marked thickening and in one of our cases this served as a clue to the diagnosis in the first year of life. In severe cases, increased porosity may also be noted in bones of the pelvis, vertebrae, ribs, clavicles and scapulae. Lateral views of the skull show an enlarged diploic space which is either finely granular or mottled, or striated. The vertical striations give the appearance of "hair standing on end," which seem to extend beyond the outer table. The earliest signs are observed in the small bones, particularly in the metacarpals and metatarsals and reveal osteoporosis and expansion of the medullary cavities, producing a rectangular instead of the normal concave appearance. The greatest opportunity for skeletal changes is in the soft and elastic bones of the infant and least in older children. Cortical thinning may be so extreme as to result in pathologic fractures.

There is no specific treatment for Cooley's anemia, and iron, copper, liver, and extracts from spleen, pancreas, adrenal, and other endocrine products, high calcium diets, large dosages of vitamin B and D, plasma and cell extracts, x-ray therapy have all been used without effect. At the suggestion of observers that this disease may in some instances repre-

sent a congenital form of malaria, we have given quinine in large dosage and have found no alteration in the blood picture. On the other hand, Caminopetros[21] observed reduction in the number of nucleated red cells and of white cells following malarial therapy.

The only measures which are of value in modifying the course of the disease are transfusions and splenectomy. Splenectomy has usually been recommended to relieve the child from the weight and pressure effects of a greatly enlarged organ. With the earlier recognition of this disease, as is sometimes possible with the aid of the roentgenogram, careful blood studies, and its suspected recurrence in an affected family, the problem that is presented concerns the desirability of removing the spleen before it becomes too large, before the liver undergoes enlargement and before extensive skeletal changes set in. The results in early cases thus far show that while splenectomy affords no cure, it prolongs life; but the choice of cases and optimal period for this operation await further study. In the case reported by Stillman and Hitzrot the patient lived for 18 years following the operation.[22]

Since the disease is only in part hemolytic and is probably fundamentally due to a deficiency of unknown hematopoietic principles or to a metabolic disturbance, splenectomy can only be expected to modify the disease slightly. However, when the hemolytic activity is extreme, splenectomy is most essential.

One of the prime indications for splenectomy has been in the reduction of the number of transfusions that are sometimes required to maintain life. In some of our cases where frequent transfusions were needed, splenectomy has succeeded in lengthening the interval between them. The elevated levels obtained by transfusions are only temporary and the blood soon drops to a point below normal at which a hematopoietic equilibrium is established and at which daily activities can be carried out without restriction. We have several children under observation who appear to be comfortable and require no transfusion for indefinite periods with hemoglobin values from 8 to 9 grams per 100 cc. of blood (50 to 60 per cent), and red counts usually between 3 to 3.5 million cells and in a few instances of from 2.5 to 3 million cells.

von Jaksch's Anemia

The question remains whether there is any further need for the term von Jaksch's anemia, particularly since the definition of Cooley's

anemia as a disease entity has removed so many cases from the earlier designation. In addition, advances in hematology have eliminated other cases which were truly secondary anemias, so that in this country at least the diagnosis of von Jaksch's anemia is at present made infrequently. In the light of modern hematological studies the greatly increased leukocyte counts with anemia noted by von Jaksch may have been leukemoid responses to infection, as well as responses in severe hemolytic anemias, deficiency anemias accompanied by infection and possibly to syphilis, especially in young infants.

English pediatricians, however, apply this term to a secondary subchronic hemolytic anemia resulting from infection, gastrointestinal and nutritional disturbances occurring in children under 3 years of age. It seems to me that this term should be reserved for a condition possessing the features originally described by von Jaksch and his contemporaries; namely, a blood disorder of infants and children which shows a reduction in hemoglobin and red cells, a pronounced leukocytosis, nucleated red cells, a greatly enlarged spleen and a smaller liver, and whose outcome is often favorable. A case should be excluded from this classification when it is now possible to assign it to a more definite category or when the etiological factor is known.

Lymphocytic Blood Pictures

Exaggerated lymphocytic reactions are especially difficult to interpret in infants and young children because a predominance of lymphocytes and a greater lability of the blood forming mechanism constitute normal features of the blood of this period. Not alone is the cause for a lymphocytosis often puzzling, but the structure and staining reaction of the cells may differ in important details from the adult patterns and, therefore, arouse suspicion of a possible blood dyscrasia. It is at this age period in particular that the differentiation between infectious mononucleosis, lymphatic leukemia and a lymphocytic response to infection is often difficult.

During the first week of life the number of polymorphonuclear leukocytes exceeds that of the lymphocytes; by the end of the first week they equalize each other, after which the lymphocytes predominate for the remainder of infancy. From the third to the fifth year these cells again approximate each other numerically and following this the granulocytes slowly increase to the adult values of about 60 per cent and lympho-

cytes decrease to from 25 to 30 per cent, levels which are usually achieved at about 12 years. Lymphocytic percentages usually do not normally exceed 60 per cent from six months to two years, 50 per cent to the end of the sixth year, 45 per cent by the eighth year and 40 per cent thereafter to adult periods. It is important to emphasize that for the true assessment of lymphocytosis absolute values must be considered. Lymphocytes may be present in normal numbers but their increased percentage when the granulocytes are suppressed and when the total count is reduced may lead to a false impression. To avoid misinterpretation, certain figures will prove of value; namely, that the maximal normal values for lymphocytes grade down from 7000 at one year to 6000 at four years and then slowly to 4000 at puberty. These are, of course, only approximate values and variations may be due to physiologic fluctuations, to differences of technique and to the chance distribution of cells.

I. INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis in children, as in adults, is an acute infectious disease occurring epidemically or sporadically and characterized by a prodromal period of malaise, anorexia, listlessness, followed by fever, pain in back of the neck, enlargement of lymph nodes, sore throat, palpable spleen, a characteristic blood picture chiefly affecting the lymphocytes. It offers an excellent prognosis. The clinical manifestations are extremely variable, and this applies to such an important diagnostic feature as lymphadenopathy.

The characteristic blood changes involve the white cells, whereas the hemoglobin and red cells remain normal during the acute stages of the disease. At about the second week of the disease with active glandular enlargement the white count ranges from 12,000 to 15,000, with values frequently below and above these extremes, and of these, the mononuclear cells average as high as 40 per cent to 80 per cent. Their classification is attended with difficulty but supravital studies have established their identity as lymphocytes although monocytes may also be somewhat increased. The blood smear shows a shift to the left of granulocytes and considerable numbers of normal small, medium and large lymphocytes. The characteristic cells are atypical and possess morphological characteristics which distinguish them from normal lymphocytes. They are larger than normal; their cellular edges are often

ragged and irregular; the cytoplasm is usually abundant and stains darker blue with the Wright stain than the normal large lymphocyte. The shade varies from a slate-color to the deep basophilia of a plasma cell and the latter is often limited to the margins of the cell. The cytoplasm contains fine or coarse azure granules and one of the most striking features is vacuolization of the cytoplasm.

The nucleus may be round, oval, kidney-shaped, occasionally divided and often eccentrically placed. The chromatin consists either of deeply staining clumped masses, as in the normal lymphocyte, or it may possess a more immature pattern in that the chromatin is composed of finer strands demarcated from the parachromatin and staining more lightly. The fenestration or holes in the nuclei of the lymphocytes which were described by Osgood[23] as peculiar to this disease are also occasionally observed.

The discovery by Paul and Bunnell that the blood serum of patients with this disease is able to clump sheep red cells in dilution considerably above the normal titer introduced an important diagnostic measure. The heterophile antibody test is practically specific, and by appropriate absorption tests it is possible to exclude the elevated titers sometimes encountered in normal persons and in those with serum sickness. While a positive serology is present in most instances, children, perhaps more than adults, frequently show a typical blood picture with a negative serology.

II. LEUKEMIA

Leukemia in childhood may for a considerable period of its course be unassociated with an enlarged spleen, lymph nodes or a leukocytosis, so that the true nature of the disease is unsuspected. The blood smear at this stage may reveal an unexplained lymphocytosis but close examination reveals that some of the lymphocytes are morphologically abnormal.[1] In this condition the immature cell varies in size from that of a small lymphocyte to one twice or a little more in size. These cells are lymphoblasts and differ from the cells of infectious mononucleosis in many respects. Lymphoblasts are usually round, more uniform in size; the cytoplasm—though basophilic—is scantier, and when vacuoles are present they are fewer and two to three times the size of those in infectious mononucleosis. The essential diagnostic feature rests, however, in the nucleus where, instead of masses of dense basichromatin as

found in the normal lymphocyte, the chromatin stains lightly, is finely granular, stippled or sieve-like, and shows the presence of nucleoli. The nuclei of the immature cells found in infectious mononucleosis on the other hand possess a greater condensation of chromatin.

III. CHRONIC NON-SPECIFIC INFECTIOUS LYMPHOCYTOSIS

Perhaps of greater importance clinically than either infectious mononucleosis or leukemia is the occurrence of a lymphocytosis in childhood which is especially common in the early years of life and which cannot be assigned to either of these categories or to other causes producing a similar blood reaction, such as influenza or typhoid fever. It is undoubtedly associated with a low grade infection, often of the upper respiratory passages and sinuses, and for weeks and months anorexia, listlessness, irritability, easy fatigability, and occasionally paraümbilical pain are common complaints. Physical examination reveals a slight reddening of the fauces, occasionally a postnasal discharge; infrequently palpable superficial lymph nodes of small size, especially in the cervical region, and the edge of the spleen may or may not be felt.

Examination of the blood shows a mild anemia affecting the hemoglobin more than the red cells; a white count from 6,000 to 15,000 of which the lymphocytes average from 50 per cent to 80 per cent; and the Paul-Bunnell test is negative. Examination of the lymphocytes reveals that they are in the main of the small and intermediate variety, that the nucleus consists of heavy chromatin masses like the normal lymphocyte but that the cytoplasm is scanty and basophilic. As is common in the blood smear of all children, an occasional cell is of the large variety and possesses a moderate basophilia and a nucleus slightly lighter staining than the normal large lymphocyte. In effect, the entire appearance of the cells represents a shift to the left of lymphocytes comparable to that of polymorphonuclear cells during infection. I believe the term which best describes this condition is chronic non-specific infectious lymphocytosis.

These cases give no antecedent history resembling infectious mononucleosis even though a few cells resemble the abnormal lymphocytes of that condition. There is no ground for regarding blood responses of this type which are usually based on infection as cases of infectious mononucleosis. The latter term should be restricted to a definite clinical syndrome, even though its etiology is as yet unknown. Non-specific

infectious lymphocytosis runs a prolonged course during which the child is susceptible to acute infections of the ear and throat. Besides treatment of the upper respiratory infection, therapy should include large doses of iron and other anti-anemic agents which serve not alone to elevate the hemoglobin but have also been observed to expedite the restoration of a normal white cell picture.

Bone Marrow Examination by Sternal Puncture

The value of bone marrow examination in the study of blood dyscrasias has long been recognized, but because biopsy involved a surgical procedure its employment has been limited. With the demonstration that the sternum was superior to the tibia as a source of active bone marrow and that an adequate specimen could be obtained by needle aspiration, bone marrow studies are now commonly carried out when the blood smear is found to be inadequate in diagnosis.

In infants and children bone marrow studies have been extremely valuable because the peripheral blood does not always completely mirror the extent of the disturbance. While normal data for the cellular content of bone marrow in early ages are still limited, certain qualitative and gross quantitative alterations can be readily ascertained.

It has already been stated that leukemia in childhood may for a period reveal no typical changes but bone pains, but an anemia more severe than can be accounted for by rheumatic fever leads to the suspicion of a blood dyscrasia. At a time when the white cells show very few if any changes in the peripheral blood, the bone marrow may be completely replaced by the blast cells of leukemia.

In diseases of abnormal lipoid metabolism, the sternal smear reveals the diagnostic Gaucher's cells characterized by striated or fibrillar network in the cytoplasm, or the typical foam cells of Niemann-Pick's disease. Sternal aspiration may assist in clarifying the early diagnosis of hemolytic jaundice and of Cooley's anemia by the pronounced cellularity of the bone marrow with normoblasts over 50 per cent of all cells. On the other hand, in a condition in infancy and childhood known as hypoplastic or chronic congenital aregenerative anemia, marked from birth by an anemia requiring frequent transfusion but with no effect on any other blood elements, the bone marrow shows very few nucleated red cells.

When sulfanilamide or sulfapyridine is administered over prolonged

periods, granulopoietic depression may occur with extremely low leukocyte counts. Quantitative measurements reveal a diminished cell content with a differential picture which varies from an almost complete suppression of all granulocytic elements to a maturation arrest at one of the earlier developmental levels. Further treatment should be controlled by marrow studies which include a qualitative and quantitative survey of both red and white cells.

Acute purpura occurs more commonly in infants and children and the chronic form more in adults. In children it is often ushered in by an infection, and spontaneous recovery is frequent without repetition of the episode. However, chronic cases usually and eventually require splenectomy. In purpura a hyperplasia of megakaryocytes is observed in the bone marrow, but separation of platelets from their cytoplasm is not observed. Splenectomy probably removes an inhibiting factor and following operation the megakaryocytes are reduced to more normal levels. It has been stated[24] that a diminution in the megakaryocytes serves as a contraindication to splenectomy and, if corroborated by further data, this will constitute an important guide to the selection of cases for operation.

Conclusion

Recent contributions in hematology have thrown a great deal of light upon the interplay of forces which maintain blood equilibrium. The diverse blood pictures outlined in this presentation indicate that certain essential hematopoietic factors are still unknown and await discovery. The detection of blood disturbances and discernment of the finer diagnostic morphologic details of reacting blood cells lie within the province of every practitioner by the painstaking use of simple instruments and techniques. In infancy and childhood the observations must, however, be interpreted with reference to the changing blood levels accompanying normal growth. With the guiding principle that anemia represents a symptom rather than a disease, and by a diligent search for a deficiency or other causative factor, rational treatment can then be instituted by the judicious administration of the few but reliable anti-anemic agents.

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